

JUSTIFICATION FOR THE AMENDMENTS

Justification for the amendments is as follows. The amendments are made to further clarify the subject matter being claimed. Support for the amendment of claims 1, 12, 13, and 29-31 can be found throughout the specification, e.g., at paragraph [0044]. Support for the amendment of claims 16, 27, 28, and 36 can be found throughout the specification, e.g., at paragraph [0016].

Claims 9-11, 17-26, 34-35, 37-38, and 46-47 are canceled herein without prejudice to their renewal. Applicants specifically reserve the right to prosecute the subject matter of the canceled claims in continuing or divisional applications.

No new matter is introduced by any of these amendments, and entry of the amendments is respectfully requested.

## **REMARKS**

### **I. Claim Status**

Claims 1-47 were originally filed and were subject to restriction. Applicants elected Group 1, claims 1-36 and 39-45, for prosecution. In an amendment filed 5 September 2008, Applicants amended claims 1-3, 9-11, 16, 19, 21, 22 and 28, added new claims 48 and 49, and canceled claims 6-8 and 39-45 without prejudice to their renewal. The Examiner has withdrawn claims 17, 18, 34, 35, 46 and 47 from consideration based on election of species for examination. In a request for continued examination, Applicants amended claims 1, 10, and 11, and canceled claims 2-5 without prejudice. Claims 1, 9-16, 19-33, 36, 48 and 49 are the subject of the present action.

Herein, claims 1, 12, 13, 16, 27-31, and 36 are amended and claims 9-11, 17-26, 34-35, 37-38, and 46-47 are canceled without prejudice to their renewal. Thus, claims 1, 12-16, 27-33, 36, and 48-49 are pending.

### **II. Summary of Examiner Interview**

Applicants thank Examiner Ogunbiyi for the courtesy extended to Christopher Turner (Reg. No. 45,167) and Christopher Jacob (Reg. No. 59,938) during an in-person interview held on 9 December 2009 to discuss the present application. During the interview, the outstanding rejections were discussed and the Examiner provided suggestions for amendments to the claims in order to overcome the outstanding rejections. No exhibit was shown, nor was any demonstration conducted.

### **III. Rejections Withdrawn**

Applicants appreciate reconsideration and withdrawal of the following rejections made in the previous Office Action.

#### **A. *Double Patenting***

The Examiner withdrew the provisional rejection of claims 1-5, 9, 10, 11-15, 19-21, and 23-27 under 35 U.S.C. §101 as claiming the same invention as that of claims 1-9, 10, 11-15, 17-24, and 34-56 of co-pending Application No. 11/348,294.

***B. Rejections under 35 U.S.C. §102***

The Examiner withdrew the rejection of claims 1-5, 9-16, 19, 21-25, and 48-49 under 35 U.S.C. §102(e) as being anticipated by Klaus et al., U.S. Patent Application Publication No. 2003/0153503 (Klaus et al.), as evidenced by Pace et al. (2000, Experimental Hematology 28:283-293) (Pace et al.).

***C. Rejections under 35 U.S.C. §103***

The Examiner withdrew the rejection of claims 1-5, 9-16, 19, 20, 21-25, and 48-49 under 35 U.S.C. 103(a) as being unpatentable over Klaus et al., Pace et al., and Tung et al., International Publication No. WO 97/12855 (Tung et al.).

The Examiner withdrew the rejection of claims 1-5, 9-16, 19, 21-33, 36 and 48-49 under 35 U.S.C. 103(a) as being unpatentable over Klaus et al., Pace et al., and Bohmer et al., International Publication No. WO 01/12784 (Bohmer et al.).

**IV. Double Patenting**

The Examiner maintained the provisional rejection of claim 16 under 35 U.S.C. §101 as claiming the same invention as that of claim 16 of co-pending Application No. 11/348,294.

As co-pending Application No. 11/348,294 is now abandoned, the provisional double patenting rejection is rendered moot. Applicants respectfully request withdrawal of the provisional double patenting rejection of claim 16 under 35 U.S.C. §101.

**V. New Rejections**

***A. Double Patenting***

The Examiner provisionally rejected claims in the present application on the ground of non-statutory obviousness-type double patenting in view of co-pending applications as outlined below:

1. Claims 1, 9-16, 19, and 21-27 were provisionally rejected as being unpatentable over claims 1-9, 10, 11-16, 17-24, and 34-56 of co-pending Application No. 11/348,294.

2. Claims 1, 9-16, 19, 21-27, 28-33, and 36 were provisionally rejected as being unpatentable over claims 1-9, 10, 11-16, 17-24, and 34-56 of co-pending Application No. 11/348,294 in view of Bohmer et al., WO 01/12784 (22 February 2001).

As co-pending Application No. 11/348,294 is now abandoned, the provisional non-statutory obviousness-type double patenting rejection is rendered moot and Applicants respectfully request withdrawal of the rejection in view of this application.

***B. Rejections under 35 U.S.C. §112***

**Enablement**

The Examiner rejected claims 28-33 and 36 under 35 U.S.C. §112, 1<sup>st</sup> paragraph, because the specification,

while being enabling for a method for increasing the level of fetal hemoglobin levels in a subject, the method comprising administering to a population of hematopoietic stem cells, BFU-E, or bone marrow cells, a hypoxia inducible factor (HIF) prolyl hydroxylase inhibitor which increases expression of the gene encoding gamma-globin and transfusing the gamma globin expressing cells into the subject, does not reasonably provide enablement for said method comprising administering to a population of other types of cells ....” (Office Action, section 8, page 14.)

Claim 28 has been amended to recite in relevant part “administering *ex vivo* to a population of cells derived from bone marrow....” Claims 29-33 and 36, which depend directly or indirectly from claim 28, also recite “a population of cells derived from bone marrow.” As the specification is enabled for the method recited in claims 28-33 and 36, Applicants respectfully request the rejection of these claims under 35 U.S.C. §112, 1<sup>st</sup> paragraph for lack of enablement be withdrawn.

**Definiteness**

The Examiner rejected claims 25-27 under 35 U.S.C. §112, 2<sup>nd</sup> paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner stated that “recitation of the broader limitation of increasing endogenous gamma-globin ... in any type of cell followed by the recitation of a narrower limitation that the ...expression of the gene coding gamma-globin is increased in either of two types of specific cells i.e. hematopoietic stem cells or blast-forming erythroid (BFU-E) cells renders the claim indefinite.” (Office

Action, section 9, pages 16-17.) As claims 25 and 26 are canceled above, the rejection is moot with respect to these claims.

Claim 27 has been amended to depend from claim 1 and recites “[t]he method of claim 1, wherein the bone marrow-derived cell or population of cells is selected from the group consisting of hematopoietic stem cells and blast-forming unit erythroid (BFU-E) cells.” Claim 1 is amended to recite in relevant part “wherein the compound increases expression of the gene encoding  $\gamma$ -globin in a bone marrow-derived cell or population of cells in the subject.” Thus, claim 1 recites that the compound increases  $\gamma$ -globin expression in a bone marrow-derived cell, and claim 27 further limits the bone marrow-derived cell to a hematopoietic stem cell or BFU-E cell. Thus, claim 27 clearly sets forth the metes and bounds of the subject matter being claimed.

As claims 25 and 26 are canceled and claim 27 is not indefinite, Applicants respectfully request the rejection of this claim under 35 U.S.C. §112, 2<sup>nd</sup> paragraph, be withdrawn

**C. *Rejections under 35 U.S.C. §102***

Claims 1, 9-16, 19, 21-27 and 48-49 were rejected under 35 U.S.C. §102(e) as being anticipated by Klaus et al., U.S. Patent Application Publication No. 2003/0153503, as evidenced by Pace et al. (2000, Exp Hematol 28:283-293), Perrine et al. (1989, Blood 74:454-459), and Ley et al. (1985, Annu Rev Med 36:485-498). The Examiner stated

Klaus teaches a method for increasing endogenous erythropoietin *in vitro* and *in vivo* comprising administering a compound that inhibits HIF prolyl hydroxylase enzyme activity.... Erythropoietin increases the expression of the gene encoding gamma globin thus increasing the level of fetal hemoglobin as evidenced by Pace et al. .... Thus, said method of increasing endogenous erythropoietin of Klaus et al. will increase endogenous gamma globin and thus increase fetal hemoglobin absent evidence to the contrary. It is known in the art that expression of the gene encoding gamma globin inherently and normally occurs in erythroid progenitor cells such as BFU-E cells as evidenced by Perrine et al. ... and/or hematopoietic/erythroid bone marrow cells ... (see Ley et al..... (Office Action, section 10, page 18.)

As claims 9-11, 19, and 21-26 are canceled above, the rejection is moot with respect to these claims.

Claim 1 as amended above recites “[a] method for treating a subject having a hemoglobinopathy, the method comprising administering to the subject in need thereof a compound, wherein the compound inhibits hypoxia-inducible factor (HIF) prolyl hydroxylase and wherein the compound increases

expression of the gene encoding  $\gamma$ -globin in a bone marrow-derived cell or population of cells in the subject.” The present specification demonstrates that compounds that inhibit HIF prolyl hydroxylase (i.e., HIF PH inhibitors or HPIs) directly increase  $\gamma$ -globin gene expression in bone marrow-derived cells and increase the proportion of fetal hemoglobin relative to non-fetal hemoglobin produced by bone marrow-derived cells. (See, e.g., Examples 4-7.) The specification also demonstrates that the effect of HPIs on  $\gamma$ -globin expression does not involve erythropoietin as an intermediary. (See, e.g., Example 4.)

Klaus et al. discloses a method of increasing endogenous erythropoietin in a subject and methods of treating anemia thereby. Klaus et al. is silent with respect to increasing  $\gamma$ -globin or treating hemoglobinopathies. The Examiner alleges that such an increase in endogenous erythropoietin would have inherently increased expression of the gene encoding gamma globin as evidenced by Pace et al. However, Pace et al. only make a statement in the abstract and in the introduction that “several pharmacological agents are known to reverse the switch resulting in  $\gamma$  gene reactivation and fetal hemoglobin (HbF) production” and include in a subsequent list of such agents “cytokines (erythropoietin)” with a citation to Al-Khatti et al. (1987) N Engl J Med 317:415. Pace et al. provide no teaching in support of this assertion. Contrary to this statement in Pace et al., Al-Khatti et al. only show that providing “pulsed treatments with high doses of recombinant human erythropoietin to baboons” stimulated increased levels of reticulocytes containing fetal hemoglobin. Further, subsequent studies revealed high doses of recombinant erythropoietin only induced fetal hemoglobin indirectly “by triggering kinetics of rapid erythroid regeneration” resulting in “transient increases of hemoglobin F-containing cells (F cells) in the peripheral blood.” (See, e.g., Stamatoyannopoulos et al. (1990) Am J Pediatr Hematol Oncol 12(1):21-26 in the abstract.) Thus, there is no evidence that increasing endogenous erythropoietin levels would increase expression of  $\gamma$ -globin in bone marrow-derived cells. As such Klaus et al. as evidenced by Pace et al. do not anticipate the present claims, both with respect to increasing endogenous  $\gamma$ -globin expression and treating hemoglobinopathies in a subject in need.

Although it may be known by those of skill in the art that expression of the gene encoding gamma globin normally occurs in erythroid progenitor cells such as BFU-E cells, as evidenced by Perrine et al., and/or hematopoietic/erythroid bone marrow stem cells, as evidenced by Ley et al., this knowledge does not further the argument that the present claims are anticipated by Klaus et al. Neither Perrine et al. nor Ley et al. teach or suggest that increasing endogenous erythropoietin, as taught by Klaus et al., would increase endogenous  $\gamma$ -globin expression in these cell types. As such, Klaus et al. as evidenced by Perrine et al. and/or Ley et al. do not anticipate the present claims.

As one of skill would not have anticipated the method of increasing endogenous erythropoietin of Klaus et al. to increase endogenous  $\gamma$ -globin and thus increase fetal hemoglobin, thereby providing a method to treat hemoglobinopathy in a subject, the methods of Klaus et al. do not anticipate the present claims. As claims 9-11, 19, and 21-26 are canceled, and claims 1, 12-16, 27, and 48-49 are not anticipated by Klaus et al., Applicants respectfully request the rejection of these claims under 35 U.S.C. §102(e) as being anticipated by Klaus et al. as evidenced by Pace et al., Perrine et al., and Ley et al. be withdrawn.

***D. Rejections under 35 U.S.C. §103***

Claims 1, 9-16, 19, 21-27, 28-33, 36, and 48-49 were rejected under 35 U.S.C. §103(a) as being obvious over Klaus et al., U.S. Patent Application Publication No. 2003/0153503, as evidenced by Pace et al. (2000, Exp Hematol 28:283-293), Perrine et al. (1989, Blood 74:454-459), and Ley et al. (1985, Annu Rev Med 36:485-498), in view of Bohmer et al., International Publication No. WO 01/12784. The Examiner's statement regarding the teaching of Klaus et al. as evidenced by Pace et al., Perrine et al., and Ley et al. is as set forth above. The Examiner further stated

Klaus et al. ... does not teach administering the HIF prolyl hydroxylase inhibitor to a population of cells and transfusing the gamma globin expressing cells into the subject. Bohmer et al. teaches a method for increasing the level of fetal hemoglobin in a subject having abnormal hemoglobin such as beta thalassemia and sickle cell syndrome such as sickle cell trait and sickle cell anemia comprising administering to a population of cells (such as hematopoietic stem cells) an agent which increase the number of fetal hemoglobin producing cells (resulting from increased expression of the gene encoding gamma globin) and transferring said cells into the subject.... It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to modify the method of Klaus et al so as to administer *ex vivo* to a population of cells that synthesize fetal hemoglobin such as hematopoietic cells said HIF prolyl hydroxylase inhibitor of Klaus et al., thus increasing gamma globin gene expression in said cells and transfuse said cells into said subjects (subjects with abnormal hemoglobin) of Klaus et al. because Bohmer et al. teaches that the level of hemoglobin can be increased *ex vivo* and said cells can be transfused back to said subject in order to treat said abnormal hemoglobin conditions. (Office Action, section 11, page 24.)

As claims 9-11, 19, and 21-26 are canceled above, the rejection is moot with respect to these claims. For at least the reasons presented below, Applicants submit that pending claims 1, 12-16, 27-33, 36, and 48-49 are non-obvious over Klaus et al., as evidenced by Pace et al., Perrine et al., and Ley et al., in view of Bohmer et al., singly or in combination.

In *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ 2d. 1385 (2007), the U.S. Supreme Court recently restated the standard that has to be satisfied in order to make a valid rejection based on a *prima facie* case of obviousness, confirming principles set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966). Under *KSR Int'l Co.*, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the prior art reference or combination of references has to teach or suggest all of the recited claim limitations. Third, the combination has to suggest a reasonable expectation of success. The Supreme Court encouraged the application of common knowledge and common sense, and took care to guard against hindsight bias and *ex post* reasoning.

According to the Manual of Patent Examining Procedure (MPEP) §2141, “the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge.” MPEP, 8<sup>th</sup> Edition (August 2001, Latest Revision July 2008). Therefore, when applying 35 U.S.C. § 103, the following tenets of patent law must be followed: the claimed invention must be considered as a whole; the references must be considered as a whole; the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and a standard of reasonable expectation of success must be applied to determine obviousness (MPEP § 2141 II).

As stated above, Klaus et al. disclose a method of increasing endogenous erythropoietin in a subject and methods of treating anemia thereby. Klaus et al. is silent with respect to increasing  $\gamma$ -globin or treating hemoglobinopathies. Pace et al. provide no teaching that increasing endogenous erythropoietin, as taught by Klaus et al., would increase endogenous  $\gamma$ -globin expression. Thus, Klaus et al., alone or as evidenced by Pace et al., do not provide “[a] method for treating a subject having a hemoglobinopathy, the method comprising administering to the subject in need thereof a compound, wherein the compound inhibits [HIF] prolyl hydroxylase and wherein the compound increases expression of the gene encoding  $\gamma$  globin in a bone marrow-derived cell or population of cells in the subject” as recited in claim 1. Further, neither Klaus et al. nor Pace et al. teach or suggest that “administering *ex vivo* to a population of cells derived from bone marrow a hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitor” would increase expression of the gene encoding  $\gamma$ -globin as recited in independent claim 28. Perrine et al. and Ley et al. also provide no teaching or suggestion in this regard. Thus, present claims 1, 12-16, 19, 27-33, 36, and



48-49 are non-obvious over Klaus et al. taken alone or as evidenced by Pace et al., Perrine et al., and/or Ley et al.

Although Bohmer et al. provide a method for treating  $\beta$ -hemoglobinopathy that comprises culturing erythroid progenitor cells in the presence of cytokines in an amount sufficient to increase the number of fetal hemoglobin producing erythroid cells in the culture, Bohmer et al. do not teach or suggest administering "a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding  $\gamma$ -globin" to said cells as presently claimed. The only cytokine specifically taught by Bohmer et al. for use in the methods claimed therein is transforming growth factor beta (TGF- $\beta$ ). Thus, neither Klaus et al. nor Bohmer et al., alone or in combination, teach or suggest the presently claimed methods. As such, claims 1, 12-16, 19, 27-33, 36, and 48-49 are non-obvious over Klaus et al. in view of Bohmer et al.

As claims 9-11, 19, and 21-26 are canceled and claims 1, 12-16, 27-33, 36, and 48-49 are non-obvious over Klaus et al., as evidenced by Pace et al., Perrine et al., and Ley et al., in view of Bohmer et al., Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103(a) as being obvious in view of these references be withdrawn.

Claims 1, 9-16, 19, 20, 21-27, and 48-49 were rejected under 35 U.S.C. §103(a) as being obvious over Klaus et al., U.S. Patent Application Publication No. 2003/0153503, as evidenced by Pace et al. (2000, Exp Hematol 28:283-293), Perrine et al. (1989, Blood 74:454-459), and Ley et al. (1985, Annu Rev Med 36:485-498), in view of Tung et al., International Publication No. WO 97/12855. The Examiner's statement regarding the teaching of Klaus et al. as evidenced by Pace et al., Perrine et al., and Ley et al. is as set forth above. The Examiner further stated

Klaus et al. ... does not teach said method for treating a disorder associate with abnormal hemoglobin by administering said HIF prolyl hydroxylase inhibitor in combination with a hydroxyurea as a second therapeutic agent. Tung et al. teaches a method for increasing endogenous gamma globin and fetal hemoglobin in a patient (in vivo, humans), the method comprising administering to the subject an agent which increases expression of the gene encoding gamma globin .... Tung et al teaches that the agent is administered in combination with a second therapeutic agent such as hydroxyurea also known to treat abnormal hemoglobin disorders such as beta-hemoglobinopathies.... It would have been prima facie obvious to one of ordinary skill in the art at the time the instant invention was made to administer a second therapeutic agent such as hydroxyurea in combination with the HIF prolyl hydroxylase inhibitor used to treat abnormal hemoglobin in the method of Klaus et al. because the art teaches (Tung et al) that conventional agents such as hydroxyurea can be used in combination with other agents such as those used to increase endogenous gamma globin to treat abnormal hemoglobin disorders. (Office Action, section 12, page 27.)

As claims 9-11, and 19-26 are canceled above, the rejection is moot with respect to these claims. For at least the reasons presented below, Applicants submit that pending claims 1, 12-16, 27, and 48-49 are non-obvious over Klaus et al., as evidenced by Pace et al., Perrine et al., and Ley et al., in view of Tung et al., singly or in combination.

Although Tung et al. provide butyrate prodrugs and their use, alone or in combination with hydroxyurea, for increasing  $\gamma$ -globin and fetal hemoglobin, Tung et al. do not teach or suggest administering “a HIF prolyl hydroxylase inhibitor which increases expression of the gene encoding  $\gamma$ -globin.” Tung et al. is also silent with respect to endogenous erythropoietin alone or in combination with other agents. Thus, neither Klaus et al. nor Tung et al., alone or in combination, teach or suggest the presently claimed methods. Further, there is no suggestion or motivation to combine the teachings of Klaus et al. with respect to increasing endogenous erythropoietin and treatment of anemia, taken alone or in view of Pace et al., Perrine et al., and Ley et al., with the teachings of Tung et al. with respect to increasing  $\gamma$ -globin using butyrate prodrugs. As such, claims 1, 12-16, 27, and 48-49 are non-obvious over Klaus et al. in view of Tung et al.

As claims 9-11, 19, and 21-26 are canceled and claims 1, 12-16, 27, and 48-49 are non-obvious over Klaus et al., as evidenced by Pace et al., Perrine et al., and Ley et al., in view of Tung et al., Applicants respectfully request that the rejection of these claims under 35 U.S.C. §103(a) as being obvious in view of these references be withdrawn.

**CONCLUSION**

In view of the foregoing, Applicants submit that the claims are fully in condition for allowance and request early notification to that effect.

**Applicants claim small entity status under 37 C.F.R. 1.27.**

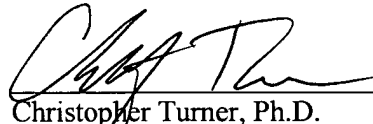
The Commissioner is hereby authorized to charge the total of the fees due in this communication to Deposit Account No. 50-0811, referencing Docket No. FP0617 US.

Please call Applicants' representative at 415-978-1745 with any questions regarding the present communication or the above-identified application.

Respectfully submitted,

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By:

  
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